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C_3-Symmetric chiral trisimidazoline: the role of a third imidazoline and its application to the nitro Michael reaction and the α-amination of β-ketoesters

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ABSTRACT

We describe the necessity of the C_3-symmetry and the role of a third imidazoline of trisimidazoline **3**, which was recently developed by us as a new entry of organocatalyst. The utility of **3** as a Brønsted base catalyst in the nitro Michael reaction and the α-amination of β-ketoesters was shown, and the recyclability of the catalyst was also demonstrated.

1. Introduction

The design of a new catalyst for asymmetric reactions is one of the key challenges and a highly important task in organic chemistry.[1] In the design of a new catalyst scaffold, molecular symmetry plays one of the powerful guidelines. It often simplifies the transition states and reduces the number of the diastereomeric reaction sites to produce a favorable effect for enantioselectivity. Therefore, C_2-symmetric molecules have been widely found in both chiral ligands for metal catalyzed reactions and asymmetric organocatalysts.[2] Compared to C_2-symmetric molecules, the studies on utilization of threefold symmetric molecules, C_3-symmetric molecules, are less commonly appeared, but various C_3-symmetric molecules were interestingly developed for chiral ligands in metal catalyzed reactions.[3,4] Their appealing structures have also been applied to molecular recognitions and material sciences as well as chiral ligands. However, there are very few reports on their utilization as asymmetric organocatalysts.[5]

In this context, we have recently reported a C_3-symmetric chiral trisimidazoline **3** as a new entry of organocatalyst.[6,7] We evaluated monoimidazoline **1**, bisimidazoline **2**, and trisimidazoline **3** as Brønsted base catalysts[8] for the enantioselective conjugate addition of α-substituted β-ketoesters to nitroolefins and found that C_3-symmetric chiral trisimidazoline **3** was the most effective (Fig. 1). The newly developed trisimidazoline **3** was regarded as a pioneering successful example of C_3-symmetric molecules for organocatalysts. However, the necessity of the C_3-symmetry and the role of the third imidazoline still remained to be clarified, though these points were very intriguing.

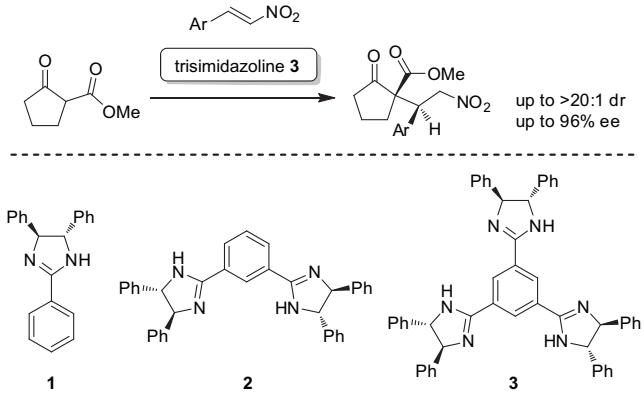

Fig. 1. Imidazoline catalysts **1**–**3** and nitro Michel reaction catalyzed by **3**.

In this paper, we describe the necessity of the C_3-symmetry of trisimidazoline **3** based on the study comparing the reactivity and the selectivity between trisimidazoline **3** and bisimidazoline **2**. In addition, to demonstrate the utility of **3** as a novel Brønsted base catalyst, the substrate scope of the nitro Michael reaction of β-ketoesters[9,10] and the application to the asymmetric α-amination of β-ketoesters[11] with di-*tert*-butyl azodicarboxylate are described. The recyclability of catalyst **3** was also investigated. These detailed

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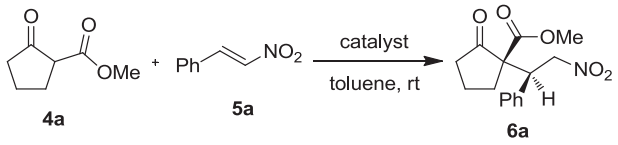
studies about **3** are valuable because C_3-symmetric trisimidazoline **3** possess a novel scaffold achieving the first highly enantioselective reaction using imidazolines as organocatalysts.

2. Results and discussion

2.1. The study on the necessity of C_3-symmetry

In our previous report, the three imidazoline catalysts, such as monoimidazoline **1**, bisimidazoline **2**, and trisimidazoline **3**, were evaluated in the nitro Michael reaction of the methyl 2-oxocyclopentanecarboxylate (**4a**) to the β-nitrostyrene (**5a**). The results are again listed in Table 1. Thus, monoimidazoline **1** produced an almost racemic product in 29% yield (entry 1, 1% ee). In the case of C_2-symmetric bisimidazoline **2**, the yield and the diastereoselectivity of the product **6a** were good, but the enantioselectivity was moderate (entry 2, 61% ee). The C_3-symmetric trisimidazoline **3** was found to provide the best yield with good diastereo- and enantioselectivity (entry 3, 89% ee). Additionally, an increase in the loading of **2** and a reduction of **3** did not have a significant influence on the selectivity: 7.5 mol % of **2** afforded **6a** in 67% ee (entry 4) and 2.5 mol % of **3** afforded **6a** in 90% ee (entry 5). These results showed that the number of imidazolines on the benzene ring has a significant effect on the enantioselectivity and the superiority of C_3-symmetric structure was obvious in studied catalysts.

Table 1
Comparison of imidazoline catalysts **1**–**3**[a]



Entry	Catalyst	Loading (mol %)	Yield (%) (dr)	ee (%)[b]
1[c]	**1**	5	29 (5:1)	1
2	**2**	5	91 (18:1)	61
3	**3**	5	94 (18:1)	89
4	**2**	7.5	90 (16:1)	67
5	**3**	2.5	97 (18:1)	90

[a] Unless otherwise noted, the reaction was carried out with **4a** (0.14 mmol), **5a** (0.21 mmol) and the catalyst (0.007 mmol) in toluene (0.47 mL) at room temperature.
[b] ee was determined by HPLC and ee of major diastereomer is shown.
[c] The reaction did not completed and was stopped within 72 h.

It is intriguing where the necessity of C_3-symmetric structure of the catalyst is. Therefore, to investigate this point, reactions of **4a** and **5a** with catalyst **1**–**3** in $CDCl_3$ were initially monitored using NMR spectroscopy, respectively. The comparison of conversion with equal amounts of imidazolines (trisimidazoline **3**, 5 mol %; bisimidazoline **2**, 7.5 mol %; monoimidazoline **1**, 15 mol %) is shown in Fig. 2. Apparently, the reaction rate of monoimidazoline **1** was very slow, and those of bisimidazoline **2** and trisimidazoline **3** were comparable. We assumed that at least two imidazolines should be involved in the activation of the reaction, and the C_3-symmetric structure had a small contribution on the enhancement of the reaction.

The reactions could then be considered to occur mainly at the site surrounded by two imidazolines. **3** has three sites surrounded by two imidazolines and **2** has one site, then to investigate the reaction with the same number of sites, an additional NMR study was carried out using 2.5 mol % of **3** and 7.5 mol % of **2**. As expected, there was no significant difference in the reaction rate between the reactions under the two reaction conditions, though the reaction rate using **2** was slightly faster than the reaction rate using **3** (Fig. 3).

On the other hand, as for enantioselectivity, there was certainly a difference between **2** and **3** as shown in entries 4 and 5 in Table 1.

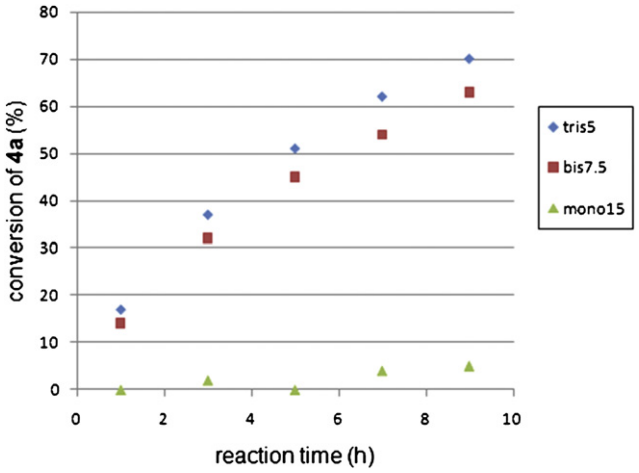


Fig. 2. Conversion of **4a** versus reaction time using catalyst **3** (5 mol %), **2** (7.5 mol %), and **1** (15 mol %).

We assumed that the lower selectivity of catalyst **2** was due to the reaction proceeding on the outside of the discussed reaction site caused by one of the two imidazolines. The slightly faster reaction with **2** observed in Fig. 3 could be also because of the reaction by one of the two imidazolines. The proceeding of the two types of reactions in bisimidazoline **2**, especially the reaction outside of the site, resulted in the decrease of the enantioselectivity of the product.

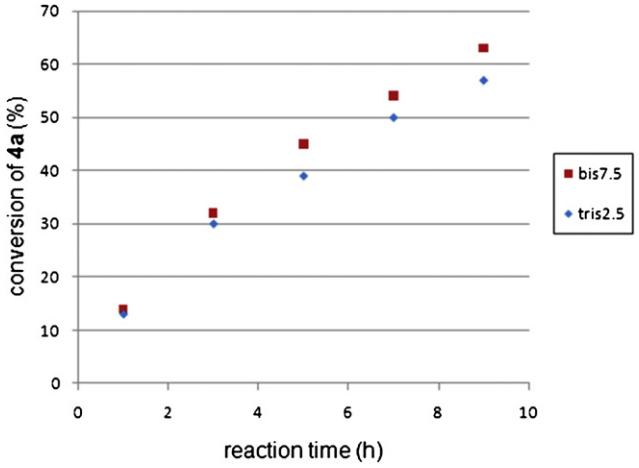


Fig. 3. Conversion of **4a** versus reaction time using catalyst **2** (7.5 mol %) and **3** (2.5 mol %).

The role of the C_3-symmetric structure was then considered as follows. Bisimidazoline structure could sufficiently enhance this conjugate addition, and the introduction of the third imidazoline ring on the 5-position of the bisimidazoline increased the enantioselectivity. Due to the N=C–N structure, namely amidine moiety, the imidazoline ring derived from chiral 1,2-diphenyl ethylenediamine has C_2-symmetric nature (Fig. 4). Therefore, three imidazolines can

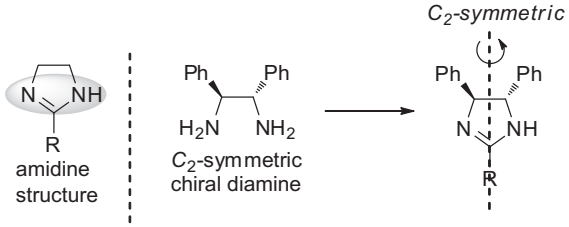


Fig. 4. C_2-symmetric nature of imidazoline.

make three equally-aligned reaction sites surrounded by two imidazolines (Fig. 5). By depressing undesirable reactions catalyzed by one imidazoline, the better chiral environment was provided.

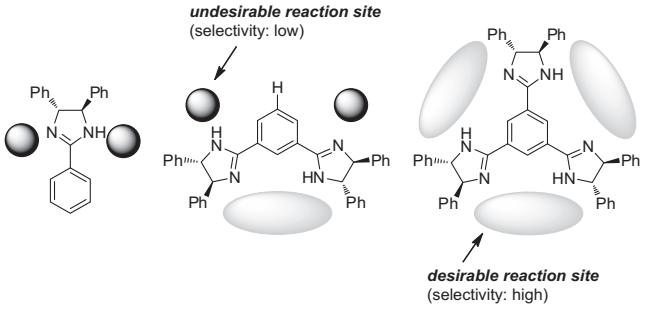


Fig. 5. Difference of reaction site.

From this consideration, to depress the reactions concerning only one imidazoline, the introduction of a bulky substituent at the 5-position of bisimidazoline also seemed to be effective. Actually, the reaction of **4a** and **5a** using bisimidazoline analogue **7**,[12a] which possesses a *tert*-butyl substituent, increased the enantioselectivity of the product to 79% ee[13] However, the selectivity with **7** was still lower than that with trisimidazoline **3** (Fig. 6). Therefore, it is concluded that the architecture of the C_3-symmetric molecule provides a superior approach to utilize the symmetric nature of the imidazoline effectively.

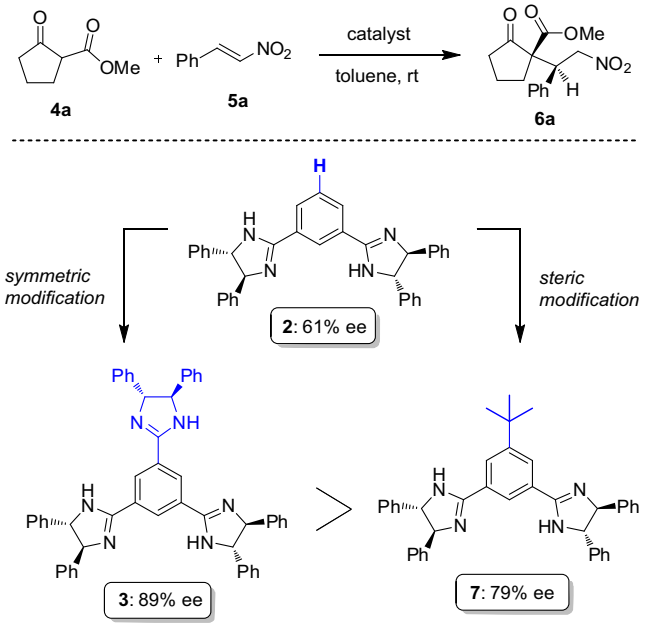


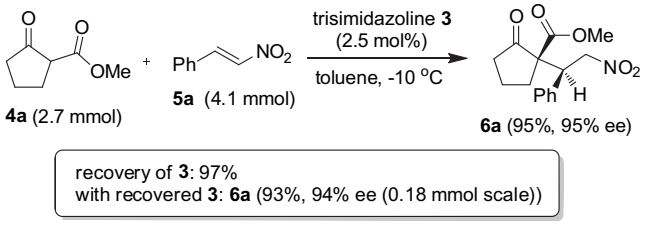
Fig. 6. Effect of the catalyst structure.

2.2. The study on the utility of trisimidazoline 3

As described in introduction section, C_3-symmetric trisimidazoline **3** had achieved the first highly enantioselective organocatalytic reaction using imidazolines as a chiral unit. This result was valuable because despite attractive properties of imidazolines, such as the basicity, nucleophilicity and the Brønsted acidity of their salts, their utilizations as organocatalysts have not been significantly explored:[12] There are only a few asymmetric reactions using imidazolines as an organocatalyst, such as the acid catalysts for the Diels–Alder reactions[12a,b] and the nucleophilic base catalysts for the Morita Baylis–Hillman reaction,[12c] in which no high enantioselectivity had been achieved. Therefore, from the view point of an organocatalyst using imidazolines, the utility of trisimidazoline **3** was interesting. To investigate the further aspect of trisimidazoline **3**, following experiments were then performed.

The detail of the generality of the nitro Michael reaction of β-ketoesters to nitroolefins with trisimidazoline **3** was initially investigated. The substrate scope coupled with previous results was shown in Table 2. The reaction of cyclic β-ketoester **4a** with various nitroolefins **5a**–**j** having electron-rich, electron-poor, bulky, and hetero aromatics afforded the desired products in high yields with good diastereo- and enantiostereoselectivity (entries 1–10). The steric and electronic properties of the substituents on aromatic rings have little effect on the stereoselectivities. Not only aromatic nitroolefins but also aliphatic one, such as isobutyl substituted nitroolefin **5k**, were found to be applicable, though 10 mol % of the catalyst loading and 3 equiv of the nitroolefin were necessary, due to the low reactivity of **5k** (entry 11). The indanone carboxylate **4b** and the tetralone carboxylate **4c** were also applicable (entries 12 and 13) as previously reported. On the other hand, the reaction using methyl acetoacetate (**4d**), acyclic β-ketoester, showed moderate enantioselectivity compared to cyclic ones (entry 14). This unexpectedly reduced selectivity could suggest the importance of the structure of the β-ketoesters in our reaction system: the cyclic β-ketoesters were more suitable substrates for high selectivity.

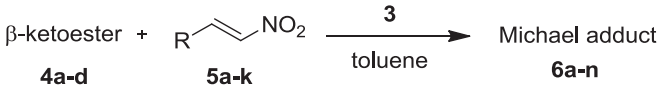
Our next interest was the recyclability of the trisimidazoline **3**. When the reaction of **4a** (2.7 mmol) and **5a** (4.1 mmol) with trisimidazoline **3** (2.5 mol %) was performed, **6a** was obtained in the high yield and the selectivity as well as the reaction of 0.14 mmol scale (Scheme 1). In this reaction, we did not observe decomposition of catalyst **3** (judged by TLC) and 97% of catalyst **3** was recovered by SiO_2 column chromatography. Recovered **3** also gave a good result in the reaction of **4a** and **5a** (93%, 94% ee).

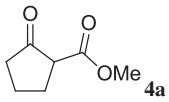
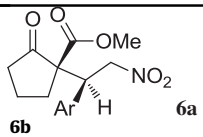
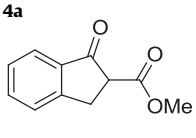
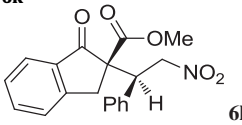
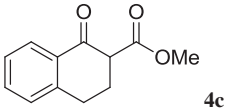
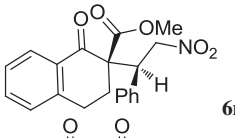
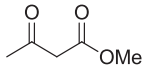
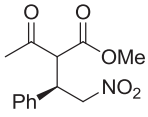


Scheme 1. A mmol scale reaction and recyclability of **3**.

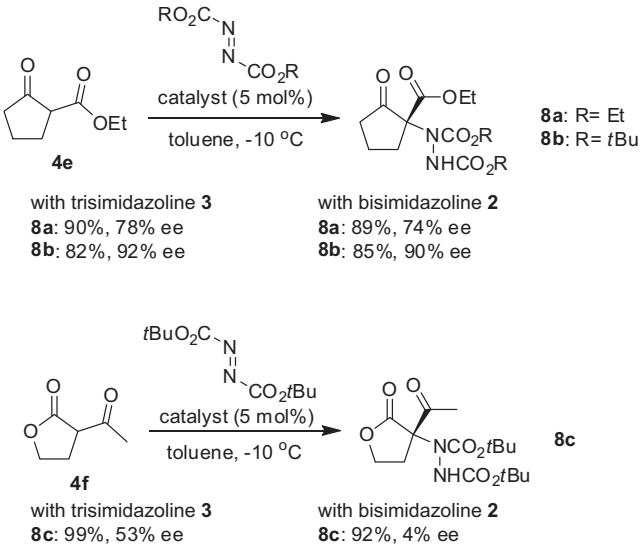
As described above, trisimidazoline **3** effectively worked in conjugate addition of β-ketoesters. Therefore, we assumed that another type of asymmetric reaction using β-ketoesters with an electrophile should be possible with **3**. The asymmetric α-amination of β-ketoesters was then applied, to explore the utility of **3** as an organocatalyst (Scheme 2). When trisimidazoline **3** was employed to the reaction of the β-ketoester **4e** and diethyl azodicarboxylate, the aminated product **8a** was expectedly produced in moderate selectivity (78% ee). More bulky di-*tert*-butyl azodicarboxylate was found to give the corresponding product **8b** more selectively (82%, 92% ee). This is promising result of trisimidazoline **3** as Brønsted base catalyst for the reaction using β-ketoesters. Interestingly, bisimidazoline **2** gave the almost comparable selectivity with **4e**. This is probably because one imidazoline catalyzed reaction could have a relatively small effect in the α-amination with **4e**. On the other hand, the reaction with 2-acetyl-γ-butyrolactone (**4f**) had again demonstrated the significant efficiency of trisimidazoline **3** compared to bisimidazoline **2**; **3** gave **8c** in moderate selectivity (53% ee),[14] by contrast, **2** gave an almost racemic product (4% ee). This difference could be explained by the high reactivity of **4f**: since the reaction with **4f** proceeded even in the absence of any catalyst (judged by TLC), one imidazoline catalyzed reaction could have a much effect.

Table 2
Generality of the conjugate addition of β-ketoesters to nitroolefins with trisimidazoline **3**[a]



Entry	4	R	6	Time (h)	Yield (%) (dr)	ee (%)[f]
1	 **4a**	Ph (**5a**)	 **6a**	48	95 (>20:1)	95
2[b]	**4a**	4-$MeOC_6H_4$ (**5b**)	**6b**	85.5	94 (>20:1)	93
3	**4a**	4-MeC_6H_4 (**5c**)	**6c**	47	89 (>20:1)	93
4	**4a**	4-ClC_6H_4 (**5d**)	**6d**	24	91 (>20:1)	96
5[b]	**4a**	4-FC_6H_4 (**5e**)	**6e**	28.5	95 (>20:1)	94
6	**4a**	3-$MeOC_6H_4$ (**5f**)	**6f**	31	98 (20:1)	93
7[b]	**4a**	2-MeC_6H_4 (**5g**)	**6g**	70	79 (16:1)	94
8	**4a**	2-BrC_6H_4 (**5h**)	**6h**	45	93 (>20:1)	93
9	**4a**	2-ClC_6H_4 (**5i**)	**6i**	75.5	96 (>20:1)	93
10	**4a**	2-thienyl (**5j**)	**6j**	48	95 (>20:1)	90[g]
11[b,d,e]	**4a**	Isobutyl (**5k**)	**6k**	139	73 (>20:1)	80
12	 **4b**	Ph (**5a**)	 **6l**	42.5	99 (4:1)	74[h]
13[c,d]	 **4c**	Ph (**5a**)	 **6m**	92	71 (>20:1)	89
14[e]	 **4d**	Ph (**5a**)	 **6n**	65	75 (1:1)	65

[a] Unless otherwise noted, the reaction was carried out with **4** (0.14 mmol), **5** (0.21 mmol) and **3** (0.007 mmol) in toluene (0.47 mL) at −10 °C.
[b] The reaction was carried out at 0 °C.
[c] The reaction was carried out at room temperature.
[d] The reaction was carried out with 10 mol % of **3**.
[e] The reaction was carried out with 3 equiv of **5**.
[f] ee was determined by HPLC and ee of major diastereomer is shown.
[g] Absolute and relative configurations were not determined.
[h] Absolute configuration was not determined.



Scheme 2. α-Amination with azodicarboxylate.

3. Conclusion

In summary, the necessity of the C_3-symmetry and the role of the third imidazoline of C_3-symmetric trisimidazoline **3** were revealed by the mechanistic study. Due to the presence of the third imidazoline, the three equally-aligned reaction sites surrounded by two imidazolines were created to give high enantioselectivity. In addition, the utility of **3** as a novel Brønsted base catalyst was shown in the nitro Michael reaction and the α-amination of β-ketoesters. The recyclability of the catalyst **3** was also demonstrated. We think that this work demonstrated the efficiency of the C_3-symmetric molecules and imidazolines for the organocatalyst. Future work will be dedicated to the development of novel asymmetric reactions using trisimidazoline **3**.[15]

4. Experimental section

4.1. Materials

Unless otherwise noted, materials were purchased from commercial suppliers and were used without purification. Preparations of imidazoline catalysts **1**–**3** were reported previously.[5] The nitroolefins **5b**–**j**[16] and **5k**[10d] were prepared according to the literature procedure.

4.2. NMR experiments in Figs. 2 and 3

To a solution of β-ketoester **4a** (40.5 mg, 0.285 mmol) and imidazoline catalyst (indicated in the following Table 3) in $CDCl_3$ (0.95 mL) was added nitroolefin **5a** (63.7 mg, 0.427 mmol) at room temperature and stirred for 5 min. The resulting clear solution was placed in NMR tube. The conversion of the reaction was monitored with ^1H NMR at the indicated reaction time (1, 3, 5, 7, and 9 h) by the integration of the following peaks: δ=3.20–3.10 ppm for **4a** and 5.29–5.10 ppm for **6a**

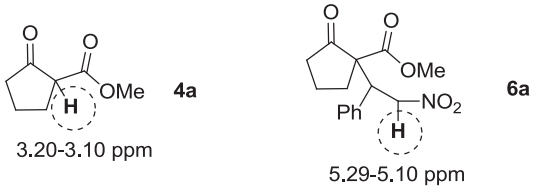
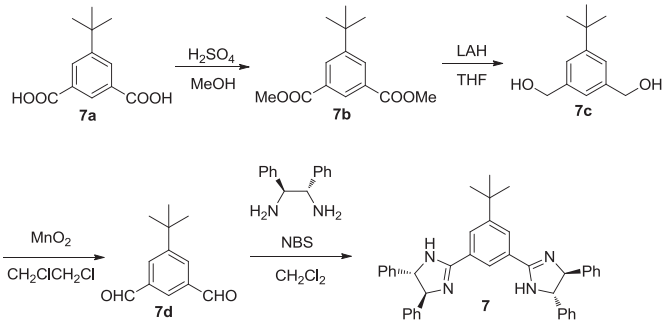


Table 3
NMR experiments

	Conversion (%)				
Conditions	1 h	3 h	5 h	7 h	9 h
Trisimidazoline **3** (5 mol %)	17	37	51	62	70
Bisimidazoline **2** (7.5 mol %)	14	32	45	54	63
Monoimidazoline **1** (15 mol %)	0.2	1.8	0	4.0	5.3
Trisimidazoline **3** (2.5 mol %)	13	30	39	50	57

4.3. Preparation of 5-*tert*-butyl-bisimidazoline 7



*4.3.1. Dimethyl 5-tert-butyl isophthalate (**7b**)*[17]. A solution of 5-*tert*-butyl isophthalic acid (**7a**) (2.17 g, 9.75 mmol) and sulfuric acid (1 mL) in MeOH (20 mL) was refluxed for 2.5 h. After being cooled to room temperature, the reaction mixture was diluted with AcOEt and washed with 10% NaOH aq and brine. Organic layer was dried over Na_2SO_4 and evaporated in vacuo to give **7b** (2.33 g, 95%) as colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ=8.51 (t, J=1.4 Hz, 1H), 8.27 (d, J=1.4 Hz, 2H), 3.95 (s, 6H), 1.38 ppm (s, 9H).

*4.3.2. (5-(tert-Butyl)-1,3-phenylene)dimethanol (**7c**)*[18]. To a suspension of $LiAlH_4$ (653.3 mg, 17.2 mmol) in THF (15 mL) was slowly added dimethyl 5-*tert*-butyl isophthalate (**7b**) (1.47 g, 5.74 mmol) in THF (15 mL) at 0 °C and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with H_2O (1 mL) and 10% NaOH aq (1 mL) at 0 °C. AcOEt (15 mL) and Celite were added to the reaction mixture and resulting mixture was stirred for 30 min. The resulting mixture was filtered through Celite and washed with AcOEt. The filtrate was concentrated in vacuo, and the residue was purified by SiO_2 column chromatography (hexane/AcOEt=2/3) to give **7c** (868.8 mg, 78%) as colorless solid. ^1H NMR (400 MHz $CDCl_3$): δ=7.32 (s, 2H), 7.20 (s, 1H), 4.69 (d, J=5.1 Hz, 4H), 1.79 (t, J=5.1 Hz, 2H), 1.33 ppm (s, 9H).

*4.3.3. 5-(tert-Butyl)isophthalaldehyde (**7d**)*[19]. To a suspension of MnO_2 (2.76 g, 31.8 mmol) in 1,2-dichroloethane (11 mL) was added (5-(*tert*-butyl)-1,3-phenylene)dimethanol (**7c**) (617.2 mg, 3.18 mmol). The reaction mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was filtered through Celite and washed with AcOEt. The filtrate was concentrated in vacuo, and the residue was purified by SiO_2 column chromatography (hexane/AcOEt=3/1) to give **7d** (470.0 mg, 78%) as colorless solid. ^1H NMR (400 MHz $CDCl_3$): δ=10.1 (s, 2H), 8.19 (s, 3H), 1.41 ppm (s, 9H).

*4.3.4. 5-tert-Butyl-bisimidazoline **7***[12a]. 5-(*tert*-Butyl)isophthalalyde (**7d**) (50.3 mg, 0.264 mmol) and (*S*,*S*)-1,2-diphenyl ethylenediamine (123.3 mg, 0.581 mmol) were dissolved in CH_2Cl_2 (6 mL) and stirred for 2 h at 0 °C under N_2. The resulting solution was added NBS (103.4 mg, 0.581 mmol) at 0 °C and the mixture was stirred overnight at room temperature. The reaction mixture was added to $Na_2S_2O_5$ aq and 5% NaOH aq, and extracted with CH_2Cl_2. Organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt/triethylamine=2/1/0.03) to give **7** (151.7 mg, 80%) as colorless solid. ^1H NMR (400 MHz $CDCl_3$): δ=8.29 (t, J=1.8 Hz, 1H), 8.15 (d, J=1.8 Hz, 2H), 7.39–7.29 (m, 20H), 5.49 (s, 2H), 5.14 (d, J=8.1 Hz, 2H), 4.33 (dd, J=1.8, 8.1 Hz, 2H), 1.42 ppm (s, 9H).

4.4. General procedure for asymmetric Michael addition of α-substituted β-ketoesters and nitroolefins

To a solution of β-ketoester **4** (1.0 equiv) and trisimidazoline **3** (0.05 equiv) in toluene (0.3 M) was added nitroolefin **5** (1.5 equiv) at −10 °C and the resulting solution was stirred at the same temperature. After the reaction was completed (judged by TLC), the reaction mixture was purified by SiO_2 column chromatography to give **6**. Preparations of Michael adduct **6a**, **6b**, **6d**, **6e**, **6g**, **6i**, **6j**, **6l**, and **6m** according to the general procedure were reported previously.[6]

*4.4.1. Methyl 1-(2-nitro-1-p-tolylethyl)-2-oxocyclopentanecarboxylate (**6c**)*[10d]. Reaction was carried out according to the general procedure with **4a** (23.7 mg, 0.167 mmol), **3** (6.2 mg, 0.0083 mmol), and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**5c**), (40.8 mg, 0.250 mmol) in toluene (0.56 mL) at −10 °C to give **6c** (45.4 mg, 89%, dr, >20:1) as colorless oil. Reaction time: 47 h. Eluent of SiO_2 column chromatography: hexane/CH_2Cl_2=1/4. $[\alpha]_{D^{28}}$ −40.0 (*c* 1.69, $CHCl_3$, 93% ee); ^1H NMR (400 MHz, $CDCl_3$): δ=7.14–7.07 (m, 4H), 5.13 (dd, J=4.2, 13.7 Hz, 1H), 4.98 (dd, J=11.0, 13.7 Hz, 1H), 4.05 (dd, J=4.2, 11.0 Hz, 1H), 3.76 (s, 3H), 2.41–2.32 (m, 2H), 2.30 (s, 3H), 2.07–1.77 ppm (m, 4H). HPLC (DAICEL CHIRALPAK OD-H, hexane/^{i}PrOH=97/3, flow rate=1.0 mL/min, detection at 207 nm): t_{minor}=16.7 min, t_{major}=21.3 min (major diastereomer); (minor diastereomer) 13.4, 17.7 min.

*4.4.2. Methyl 1-(1-(3-methoxyphenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (**6f**)*[10d]. Reaction was carried out according to the general procedure with **4a** (25.8 mg, 0.181 mmol), **3** (6.7 mg, 0.0091 mmol), and (*E*)-1-methoxy-3-(2-nitrovinyl)benzene (**5f**) (48.8 mg, 0.272 mmol) in toluene (0.60 mL) at −10 °C to give **6f** (57.1 mg, 98%, dr, 20:1) as colorless oil. Reaction time: 31 h. Eluent of SiO_2 column chromatography: hexane/CH_2Cl_2=1/4. $[\alpha]_{D^{28}}$ −33.5 (*c* 1.41, $CHCl_3$, 93% ee); ^1H NMR (400 MHz, $CDCl_3$): δ=7.24–7.20 (m,

1H), 6.83–6.80 (m, 3H), 5.15 (dd, *J*=4.0, 13.6 Hz, 1H), 5.00 (dd, *J*=11.0, 13.6 Hz, 1H), 4.04 (dd, *J*=4.0, 11.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.42–2.32 (m, 2H), 2.11–1.80 ppm (m, 4H). HPLC (DAICEL CHIRALPAK OD-H, hexane/^{i}PrOH=99/1, flow rate=1.0 mL/min, detection at 207 nm): t_{minor}=50.9 min, t_{major}=60.2 min (major diastereomer); (minor diastereomer) 40.0, 48.0 min.

*4.4.3. Methyl 1-(1-(2-bromophenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (**6h**)*[10d]. Reaction was carried out according to the general procedure with **4a** (22.4 mg, 0.158 mmol), **3** (5.8 mg, 0.0079 mmol), and (*E*)-1-bromo-2-(2-nitrovinyl)benzene (**5h**) (53.9 mg, 0.236 mmol) in toluene (0.52 mL) at −10 °C to give **6h** (54.2 mg, 93%, dr, >20:1) as colorless oil. Reaction time: 45 h. Eluent of SiO_2 column chromatography: hexane/CH_2Cl_2=1/4. $[\alpha]_{D^{25}}$ +18.1 (*c* 0.89, $CHCl_3$, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.58 (dd, *J*=1.2, 8.0 Hz, 1H), 7.52 (dd, *J*=1.6, 8.0 Hz, 1H), 7.33–7.29 (m, 1H), 7.17–7.12 (m, 1H), 5.48 (dd, *J*=3.2, 13.6 Hz, 1H), 5.07 (dd, *J*=10.8, 13.6 Hz, 1H), 4.51 (dd, *J*=3.2, 10.8 Hz, 1H), 3.75 (s, 3H), 2.52–2.48 (m, 2H), 2.26–2.08 (m, 2H), 2.00–1.89 ppm (m, 2H). HPLC (DAICEL CHIRALPAK AD-H, hexane/^{i}PrOH=90/10, flow rate=1.0 mL/min, detection at 207 nm): t_{minor}=9.3 min, t_{major}=10.7 min (major diastereomer); (minor diastereomer) 12.6, 13.0 min.

*4.4.4. Methyl 1-(4-methyl-1-nitropentan-2-yl)-2-oxocyclopentanecarboxylate (**6k**)*[10d]. Reaction was carried out according to the general procedure with **4a** (22.7 mg, 0.160 mmol), **3** (11.8 mg, 0.016 mmol), and (*E*)-4-methyl-1-nitropent-1-ene (**5k**) (61.9 mg, 0.480 mmol) in toluene (0.53 mL) at 0 °C to give **6k** (31.6 mg, 73%, dr, >20:1) as colorless oil. Reaction time: 139 h. Eluent of SiO_2 column chromatography: hexane/CH_2Cl_2=1/4. $[\alpha]_{D^{28}}$ −66.1 (*c* 1.31, $CHCl_3$, 80% ee); ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=4.89 (dd, *J*=5.8, 14.6 Hz, 1H), 4.33 (dd, *J*=4.2, 14.6 Hz, 1H), 3.71 (s, 3H), 2.95–2.90 (m, 1H), 2.64–2.58 (m, 1H), 2.49–2.26 (m, 2H), 2.07–1.92 (m, 3H), 1.61–1.42 (m, 2H), 1.08–0.99 (m, 1H), 0.91 ppm (d, *J*=6.8 Hz, 6H). HPLC (DAICEL CHIRALPAK OD-H, hexane/EtOH=98/2, 15 °C, flow rate=1.0 mL/min, detection at 207 nm): t_{minor}=10.7 min, t_{major}=13.3 min (major diastereomer); (minor diastereomer) 11.7, 12.7 min.

*4.4.5. Methyl-2-acetyl-4-nitro-3-phenylbutyrate (**6n**)*[20]. Reaction was carried out according to the general procedure with **4d** (30.7 mg, 0.213 mmol), **3** (7.9 mg, 0.0107 mmol), and *trans*-β-nitrostylene (**5a**) (95.3 mg, 0.639 mmol) in toluene (0.71 mL) at −10 °C to give **6n** (52.0 mg, 75%) as a white solid (1:1 diastereo mixture). Reaction time: 65 h. Eluent of SiO_2 column chromatography: hexane/AcOEt=3/1. $[\alpha]_{D^{27}}$ −31.3 (*c* 1.74, $CHCl_3$, 65% ee); ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.34–7.25 (m, 3H), 7.21–7.19 (m, 2H), 4.88–4.80 (m, 1H), 4.77 (d, *J*=6.0 Hz, 1H), 4.29–4.18 (m, 1H), 4.12 (d, *J*=9.8 Hz, 0.5H), 4.05 (d, *J*=9.8 Hz, 0.5H), 3.77 (s, 1.5H), 3.50 (s, 1.5H), 2.29 (s, 1.5H), 2.04 ppm (s, 1.5H). HPLC (DAICEL CHIRALPAK AD-H, exane/EtOH=95/5, 10 °C, flow rate=1.0 mL/min, detection at 207 nm): (first isomer) t_{minor}=23.7 min, t_{major}=45.7 min, (second isomer) t_{minor}=40.3 min, t_{major}=36.2 min.

4.5. α-Amination with azodicarboxylate

*4.5.1. N′N-Bis(ethoxycarbonyl)-1-hydrazino-2-oxocyclopentanecarboxylic acid ethyl ester (**8a**)*[21]. To a solution of ethyl 2-oxocyclopentanecarboxylate (**4e**) (23.7 mg, 0.152 mmol) and trisimidazoline **3** (5.6 mg, 0.0076 mmol) in toluene (0.41 mL) was added diethyl azodicarboxylate (2.2 M solution in toluene, 0.10 mL, 0.228 mmol) at −10 °C, and the mixture was stirred for 1 h at the same temperature. After the reaction was completed (judged by TLC), the reaction mixture was purified by SiO_2 column chromatography (hexane/AcOEt=2/1) to give **8a** (45.0 mg, 90%) as colorless oil. ^{1}H NMR (400 MHz, CDCl3): *δ*=6.77 (br s, 1H), 4.35–4.16 (m, 6H), 2.65–1.74 (m, 6H), 1.29–1.07 ppm (m, 9H). $[\alpha]_{D}$ ^{25} +1.92 (*c* 0.85, $CHCl_3$, 78% ee). HPLC (DAICEL CHIRALPAK AD-H, hexane/^{i}PrOH=95/5, flow rate=1.0 mL/min, detection at 207 nm): t_{minor}=25.6 min, t_{major}=22.1 min.

*4.5.2. N′N-Bis(tert-butoxycarbonyl)-1-hydrazino-2-oxocyclopentanecarboxylic acid ethyl ester (**8b**)*[11i]. To a solution of ethyl 2-oxocyclopentanecarboxylate (**4e**) (26.0 mg, 0.166 mmol) and trisimidazoline **3** (6.2 mg, 0.0062 mmol) in toluene (0.55 mL) was added di-*tert*-butyl azodicarboxylate (57.5 mg, 0.250 mmol) at −10 °C, and the mixture was stirred for 24 h at the same temperature. After the reaction was completed (judged by TLC), the reaction mixture was purified by SiO_2 column chromatography (AcOEt/CH_2Cl_2=1/15) to give **8b** (52.9 mg, 82%) as colorless oil. $[\alpha]_{D^{26}}$ −2.38 (*c* 1.23, $CHCl_3$, 92% ee); ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=6.59 (br s, 1H), 4.23 (br s, 2H), 2.59–1.96 (m, 6H), 1.52–1.44 (m, 18H), 1.28 ppm (t, *J*=7.2 Hz, 3H). HPLC (DAICEL CHIRALPAK AD-H, hexane/EtOH=95/5, flow rate=1.0 mL/min, detection at 207 nm): t_{minor}=4.9 min, t_{major}=6.0 min.

*4.5.3. N′N-Bis(tert-butoxycarbonyl)-2-hydrazino-2-acetyl-γ-butyrolactone (**8c**)*[11i]. To a solution of 2-acetyl-γ-butyrolactone (**4f**) (31.7 mg, 0.247 mmol) and trisimidazoline **3** (9.1 mg, 0.0091 mmol) in toluene (0.82 mL) was added di-*tert*-butyl azodicarboxylate (85.5 mg, 0.371 mmol) at −10 °C, and the mixture was stirred for 21.5 h at the same temperature. After the reaction was completed (judged by TLC), the reaction mixture was purified by SiO_2 column chromatography (hexane/AcOEt=2.5/1) to give **8c** (87.8 mg, 99%) as white solid. $[\alpha]_{D^{27}}$ +1.36 (*c* 1.27, $CHCl_3$, 53% ee); ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=6.80 (br s, 1H), 4.38 (m, 2H), 3.27–2.30 (m, 5H), 1.47 ppm (s, 18H). HPLC (DAICEL CHIRALPAK AD-H, hexane/EtOH=95/5, flow rate=1.0 mL/min, detection at 207 nm): t_{minor}=7.0 min, t_{major}=9.0 min.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.005.

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